## REMARKS

Upon entry of this amendment, claims 1-9 and 12-21 will be pending. Certain claims have been revised to more clearly define the invention. The amendments are supported in the specification and are believed to add no new matter.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

## CLAIM OBJECTIONS AND MISC. AMENDMENTS

Claim 8 was objected to due to a misspelling. This typographical error has been corrected.

Claims 9 and 20 have been amended so that the spelling of "NCp7" is consistent with that of claim 5.

Claim 18 was amended to improve clarity by further reciting that the template nucleic acid is RNA and that the polymerase is RNA-dependent.

In claim 20 the word "the" was deleted to improve clarity.

## REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-9, 13, 15-17, 21, 28 and 31 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

A) More specifically, the Examiner is of the opinion that the term "flWT1(GNRA)2" renders claims 13 and 16 indefinite. Applicant respectfully submits that the term "flWT1(GNRA)2" would be clear to the skilled practicioner reading the subject application. Support for the term can be found, for example, in the figure legend of Figure 2 at page 18:

*"Insertion of one or two copies of GNRA stem-loop structure was done in flWT1, a derivative of pSP/WT1..."*

In addition, Figure 2 also shows the sequence of GNRA and its insertion position in flWT1.

To expedite prosecution, claims 13 and 16 have been amended to recite specific sequences having a stem-loop structure. Support for the amendment is found in Fig. 2. Applicant respectfully submits this amendment obviates the rejection.

B) Claims 1-9, 15-17, 21-28 and 31 were asserted to be indefinite for the lack of active method steps. The Applicant respectfully submits that this rejection has been overcome by the amendments to the claims which now recite active method steps (e.g. "adding").

C) Claims 1 and 31 were considered confusing, the Examiner considering that there is a discrepancy between the preamble and the use of the term "a polymerase." Applicant submits that this rejection is overcome by the replacement of the terminology "a polymerase" by "said polymerase" in claim 1. Claim 31 has been cancelled.

D) Applicant submits that the rejections of claims 6, 16, 20 and 25 for an insufficient antecedent basis for the limitations in the claims have been overcome by amendments to claims 6, 16 and 20 and the cancellation of claim 25.

E) In claim 6 the phrase "significant" was alleged to be unclear. Applicant respectfully disagrees but, solely to expedite prosecution, this term has been deleted in the claim.

In view of these comments and amendments, Applicant respectfully requests that the Examiner withdraws the rejections under 35 U.S.C. § 112, second paragraph.

**REJECTION UNDER 35 U.S.C. § 103(A)**

Claims 1-9, 12, 14-15 and 17-21 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Legerski '891 in view of Allen '151. The Examiner asserts that

*"Legerski teaches a method of synthesis of full length cDNAs utilizing a highly processive RNA-dependent DNA polymerases ..., RNA-*

*dependent RNA polymerases as well as DNA-dependent DNA polymerases."*

The Examiner also states:

*"Legerski teaches reverse transcribing RNA in the presence of processivity inhibiting structures (col. 2, lines 56-59)".*

The Examiner acknowledges that

*"Legerski does not teach binding proteins... retroviral nucleocapsid RNA binding proteins... NCp7... reverse transcribing RNA in the presence of both inhibiting structures and increasing agents... comparing the length of the polymerase products as being measurably higher in the presence of the candidate agent than in the absence thereof... [and] does not teach a polymerization composition having a general RNA binding protein."* [emphasis added]

The Examiner considers that one of ordinary skill, at the time of the invention, would have been motivated to combine Allen et al. [which is alleged to describe: retroviral nucleocapsid RNA binding proteins and their use in increasing the processivity of reverse transcriptase; NCp7; reverse transcription of RNA (where both inhibiting structures and increasing agents are present); comparing the length of the polymerized products as measurably higher in the presence of the candidate agents as compared to the absence thereof; and a polymerization composition having a general RNA binding protein] and Legerski's method for the synthesis of full length cDNAs. The Examiner therefore considers that it would have been *prima facie* obvious to apply Allen's RNA binding proteins to Legerski's method.

The Applicant respectfully traverses this rejection as follows.

While Legerski teaches that the processivity of RNA-dependent DNA polymerases is inhibited by secondary structure, he arrives at a significantly different solution for overcoming same: cycling of temperatures and cycling of thermostable reverse transcriptase and non-thermostable but processive reverse transcriptase, thereby exploiting

*"The notion that the mRNA secondary structures may be removed by elevating the temperature of the reverse transcriptase reaction... however, although these enzymes are operative at high temperatures (55-90°), the reaction is very slow. This inefficiency can be circumvented by adding a fresh processive RT enzyme once the impediment of the secondary structure has been bypassed. Thus, the synthesis of the first strand can be continued at the lower temperature.*

*This cycling allows the alternate synthesis of the long chain at the lower temperature [37-45°C] and removal of the secondary structures at the higher temperature." (column 6, lines 15-27)*[Emphasis added]

Indeed, Legerski summarizes its teachings at column 6, between lines 50-56:

*"Thus, by exploiting a combination of (a) processive enzymes at a lower temperature to increase the length of the first strand of the cDNA and (b) thermostable enzymes at a higher temperature to remove the secondary structures formed in the first strand, the present invention provides an effective method of producing long cDNAs moieties in a reverse transcription based synthesis method."* [Emphasis added]

Further, the Applicant respectfully disagrees with the Examiner's contention that

*"Allen teaches retroviral retroviral nucleocapsid RNA binding proteins to increase the processivity of reverse transcriptase (col. 1, lines 45-67)."* [Emphasis added]

While Allen suggests a number of functions for nucleocapsid proteins, the references cited in the teachings of Allen between column 1, lines 45-67 and column 2, lines 1-22 are but mere suggestions. It is apparent that at most, Allen teaches at column 2, starting at line 15:

*"Results from these studies [mutations in RSV and MuLV nucleocapsid proteins] suggested a role for nucleocapsid during reverse transcription... and possibly during infection." [emphasis added]*

Contrarily to the allegation of the Examiner, Allen does not teach, that NCp7 or nucleocapsid protein increases the processivity of RT. It does teach however, between lines 45-61 of column 1, that nucleocapsid plays an instrumental role in annealing of tRNA primer to viral RNA, annealing the tRNA primer onto the primer binding site, and dimer formation of genomic RNA. In addition, the Applicant disagrees with the interpretation of the Examiner of the teachings of Allen that reverse transcribing RNA, where both inhibiting structures and increasing agents are present, is applicable to the present invention, since the inhibitory structures of Allen are RNA ligands which have been selected by affinity binding to nucleocapsid using the SELEX method. Of importance, these structures are not internal structures to the nucleic acid to be amplified (the template) as in the present invention, but ligands which are aimed at inhibiting and not increasing the processivity of the reverse transcriptase.

With respect to the rejection of the Examiner relying on the teachings at column 5, (lines 15-66), the Applicant believes that these teachings are significantly different from those of the

present invention since they relate to an enrichment of nucleic acid ligands which bind to HIV nucleocapsid (through affinity purification) and not an increase in the processivity of a reverse transcriptase, as per the present invention, by providing for example a RNA binding protein which enables the RT to pass through a region of secondary structure on the template it is transcribing.

Applicant therefore fails to see the motivation to combine the temperature cycling and reverse transcriptase cycling method of Legerski and the HIV RNA binding proteins of Allen, aimed at purifying inhibitors of RT, since Allen fails to provide a teaching that HIV RNA binding can increase the processivity of reverse transcriptase. Of note, the hypothetical and non-motivated combination of Legerski and Allen is considered by the Applicant to be a non-functional combination since the HIV nucleocapsid of Allen and the RNA ligands thereof, with the method of Legerski could not have increased the processivity of RT, because the nucleocapsid protein would have been competed out by the random pools of sequences of Allen to which they bind. Indeed, Allen aims at providing a nucleic acid sequence that will compete with HIV nucleocapsid with the aim of inhibiting its function, thereby providing structures which could be used as anti-HIV agents. Thus, Allen, in constradistinction to the instant invention, aims at inhibiting nucleocapsid function and not at increasing the processing of RT. In addition, Allen is strictly concerned with HIV nucleocapsid proteins and does not teach RNA binding proteins in general. Furthermore, the hypothetical combination of the nucleocapsid of Allen with the high temperature of Legerski could denature a nucleic acid binding protein of the invention, thereby negating its role in enabling an increase in the processivity of the RT.

Clearly, the combination of Legerski and Allen cannot be equated as rendering obvious the present invention, especially if one considers the fact that Legerski does not teach any binding protein overcoming the presence of secondary structures in a template RNA, but rather a cycling of temperatures, and the teachings of Allen of RNA ligands which are aimed at inhibiting nucleocapsid protein function.

In view of the newly submitted claims and of the above arguments, the Applicant respectfully urges the Examiner to reconsider the rejection of claims 1-9, 12, 14-15 and 17-21.

---

Claims 13 and 16 have been rejected under under 35 U.S.C. § 103(a) as being unpatentable over Legerski in view of Allen and in further view of Sampson (US Pat. No. 6,054,274).

The teachings of Legerski and Allen have been described previously.

The Examiner considers that Sampson teaches "flWT1(GNRA)2" at column 8, lines 56-67. The Applicant respectfully disagrees with this contention of the Examiner since the flWT1 construct having stem loops GNRA structures are not taught by Sampson. It is taught that the

> *"C(GTAA)G loop sequence conforms to the known thermodynamically stable C(GNRA)G class of loops...and stem structures are composed of standard GC base pairs and two non-standard A-G and G-A base pairs that are known to be thermodynamically stable when presented in the given sequence context..." (column 8, lines 59-65).*

Based on the fact that Sampson does not teach flWT1(GNRA)2 but rather a sequence comprising up to "500 hairpin loops structures (16 repeating signal amplification units)" and not flWT1, and in view of the arguments that the combination of Legerski and Allen results in a non-functional combination, it is respectfully requested that the Examiner withdraws his rejection of claims 13 and 16 under 35 U.S.C. § 103(a) in view of the combination of Legerski, Allen and Sampson.

---

Claims 22-28 and 31 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Legerski in view of Tabor '466. In view of the cancellation of claims 22-28 and of claim 31, this rejection has been rendered moot.

---

Claim 15 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hogrefe '997. The Examiner alleges that Hogrefe "teaches a method of selecting an agent which is capable of increasing the processivity of a DNA-dependent polymerase..." and that is would have been *prima facie* obvious to modify Hogrefe... method of selecting an agent which is capable of increasing the processivity of a DNA-dependent polymerase to include the length of the PCR product yield".

Claim 15 has been amended to state that the hybridization mixture comprises a template RNA. Applicant respectfully submits that in view of the amendment to claim 15 which relates to RNA-dependent polymerase, that the rejection of claim 15 has been overcome.

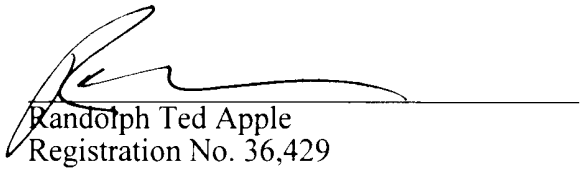
## CONCLUSIONS

The rejections of claims 1-9 and 12-28 are believed to have been overcome by the present remarks, and by the amendments to the claims. Favorable action in the form of a Notice of Allowance is requested.

In the event that there are any questions concerning the Amendment, or application in general, the Examiner is respectfully requested to telephone the undersigned so that the prosecution of the application may be expedited.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 514012000300.

Respectfully submitted,

Dated: February 3, 2003 By: 

Randolph Ted Apple
Registration No. 36,429

Morrison & Foerster LLP
755 Page Mill Road
Palo Alto, California 94304-1018
Telephone: (650) 813-5933
Facsimile: (650) 494-0792

## VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 1, 6, 8, 9, 12, 15, 18 and 20 have been amended as follows: Underlines indicate insertions and brackets "[ ]" indicate deletions.

1. (Amended) A method to increase the processivity of a RNA-dependent DNA polymerase comprising [an addition of] adding an effective amount of a general RNA binding protein to a nucleic acid polymerization mixture comprising [a] said polymerase, whereby addition of said RNA binding protein enables an increase of the processivity of said polymerase.

6. (Amended) An improved method of cDNA synthesis, the improvement consisting in [an addition of] adding a general RNA binding protein to [the] a nucleic acid polymerization mixture comprising [the] a reverse transcriptase, whereby [said] addition of [general]said RNA binding protein enables an increase of the processivity of said reverse transcriptase, thereby enabling [a significant] an increase in the production of full length cDNAs.

8. (Twice amended) The improved method of claim 6, wherein said RNA binding protein is a retroviral [nucleocasid] nucleocapsid protein.

9. (Amended) The method of claim 8, wherein said general RNA binding protein is [Ncp7] NCp7.

12. (Amended) A method to identify agents which can increase the processivity of a [DNA- or] RNA-dependent polymerase, comprising:

a) reverse transcribing a RNA having a polymerase processivity inhibiting structure in the presence of a candidate processivity increasing agent; and

b) comparing the length of the polymerized products;

wherein a potential processivity increasing agent is identified when the length of polymerized products is measurably higher in the presence of the candidate agent than in the absence thereof.

13. (Amended) The method of claim 12, wherein said RNA comprises the sequence 5'-GTAAAAACCCGCTTCGGCGGGTTTTTGCAGAGATCCCCCTCTTCGGAGGGGGA-3'

or 5'-CCAGGCCCGGAAGGCCCGGAGTAATCCGGGCCTTCCGGGCCTGGCCCCCCC-3' [is flWT1(GNRA)2].

15. (Amended) A method of selecting an agent which is capable of increasing the processivity of a [DNA- or] RNA-dependent polymerase, comprising:

a) incubating a candidate polymerase processivity increasing agent together with a polymerization mixture comprising a template RNA and an RNA-dependent polymerase; and

b) comparing the length of the polymerized products;

wherein a potential processivity increasing agent is selected when the length of polymerized products is measurably higher in the presence of the candidate agent than in the absence thereof.

16. (Amended) The method of claim 15, wherein said RNA comprises the sequence 5'-GTAAAAACCCGCTTCGGCGGGTTTTTGCAGAGATCCCCCTCTTCGGAGGGGGA-3' or 5'-CCAGGCCCGGAAGGCCCGGAGTAATCCGGGCCTTCCGGGCCTGGCCCCCCC-3' [is flWT1(GNRA)2].

18. (Amended) A polymerization processivity-increasing composition, comprising a template [nucleic acid] RNA, a RNA-dependent polymerase and a general RNA binding protein, together with a suitable polymerization buffer.

20. (Amended) The composition of claim 18, wherein said RNA binding protein is [the] chaperone protein [Ncp7] NCp7.

21. (Amended) A method to increase the processivity of a RNA-dependent RNA polymerase comprising [an addition of] adding an effective amount of a general RNA binding protein to a nucleic acid polymerization mixture comprising said RNA-dependent RNA polymerase, whereby [said] addition of said general RNA binding protein enables an increase of the processivity of said polymerase.